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10/087,996	02/28/2002	Brian Leyland-Jones	3298.1003-000	2676

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EXAMINER	
LEWIS, AMY A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,996	LEYLAND-JONES, BRIAN	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46 and 89-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-46 and 89-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-D-6

DETAILED ACTION

Status of the Case

Applicant's Amendments and remarks filed 3 March 2005, have been entered into the application. Accordingly, claims 41-46 have been amended and new claims 89-94 have been added. Therefore, claims 41-46 and 89-94, as filed 3 March 2005, are pending in this application.

Response to Arguments

Applicant's arguments filed 3 March 2005 have been fully considered but they are *not persuasive*.

1) Claims 41-46 were rejected under 35 U.S.C. 102(b) as being anticipated by Ratain et al. (Cancer Research 1993, 53: 2304-2308). This rejection is ***maintained,*** and now applied to new claim 89 and 94.

Applicant argues that Ratain et al. do not disclose the claimed invention. And additionally the amendments to the claims to include "using a *specific* metabolic phenotype to individualize treatment" (emphasis added), is further evidence that Ratain et al. does not disclose the invention. The Examiner disagrees. Ratain et al. clearly teach the claimed invention.

As stated in the previous office action, Ratain et al. teach a method of metabolic phenotyping to individualize amonafide dosage. Ratain et al. determined the acetylator phenotype of cancer patients in need of amonafide therapy, using caffeine as the probe drug and urine as the biological sample. "Urinary concentrations of an acetylated (AAMU)[3] and

nonacetylated (1X) metabolite are determined by high-pressure liquid chromatography"; and the acetylator phenotype (slow, indeterminate, or fast acetylators) is based on the molar ratio of AAMU:IX. (See Acetylator Phenotyping, p. 2304). Dosage regimen of amonafide was individualized based on this phenotype, where the initial dose levels for slow, indeterminate, and fast acetylators were 375, 300, or 250 mg/m^2 (for 5 days), respectively. (See Amonafide Dosing, p. 2304). In addition, Ratain et al. teach determining hematological toxicity by dose level by testing white blood cell counts and adjusting amonifide doseage accordingly (page 2305).

Further, including the term "specific" in the claim language does not further limit the claims, provides no cogency with respect to description of the invention and does not better define the invention.

Regarding Applicant's argument that Ratain et al. do not inherently disclose the claimed invention, the Examiner did not make an inherency argument when rejecting claims 41-46 over Ratain et al.

2) Claims 41-46 were rejected under 35 U.S.C. 102(b) as being anticipated by Wainer et al. (U.S. Patent 5,830,672). This rejection is ***maintained,*** and now applied to new claims 89 and 94.

Again, Applicant argues that Wainer et al. do not disclose the claimed invention. And additionally the amendments to the claims to include "using a *specific* metabolic phenotype to individualize treatment" (emphasis added), is further evidence that Wainer et al. does not disclose the invention. The Examiner disagrees. Wainer et al. clearly teach the claimed invention.

As stated in the previous office action, Wainer et al. teach a method for determining N-acetyltransferase (NAT2) phenotype using and enzyme linked immunosorbent assay (ELISA) kit to individualize therapy of drugs, including amonafide (col. 1, lines 8-14). The ELISA measures the molar ratio of caffeine metabolites in a urine sample (col. 3, lines 15-55; claims 1-3 and 5-10). The acetylation phenotype is based on this ratio, where patients with a ratio less than 1.80 are considered slow acetylators (col. 3, lines 55-58). Further, the method taught by Wainer et al., of using caffeine and an ELISA to determine NAT2 phenotype is the same method claimed in the instant application (see Applicant's specification pages 269-274). In addition, Wainer et al. test and compare white blood cell counts in slow vs. fast acetelyators treated with amonifide (p. 576, Fig. 2).

And as discussed above, including the term "specific" in the claim language does not further limit the claims, provides no cogency with respect to description of the invention and does not better define the invention.

3) Regarding Applicant's argument that neither Ratain et al. nor Wainer et al. teach "individualized therapy," the claims only set forth the limitation "individualizing," and nothing more specific, simply dividing patients into dosage groups depending on their acetylator phenotype therefore meets this limitiation. See further discussion in the rejection under 35 USC 112, 2nd paragraph, below.

Objection to the Drawings

Figure 25 is described in the specification (p. 66), however it is not present in the drawings filed on 4 November 2002. Appropriate correction is required.

The following new rejections will be set forth as follows:

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection:

Claims 42, 45, 46, and 90-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 42, 45, 46, and 90-93 have been added/amended to recite determining the metabolic phenotype of an individual to individualize a treatment regimen for said individual by administering amonifide as the probe substrate in order to determine a safe and therapeutically effective dose of N-(aryl substituted)-naphthalidimide compound. The element of using amonifide as the probe substrate, however, was not described in the specification. The

specification only provides methods for using caffeine as a probe substrate to determine metabolic phenotype.

Claim 94 includes determining metabolic phenotype by also including the characteristics of age, gender, and white blood cell count. The specification only provides support for using gender and white blood cell with respect to NAT2 acetylation phenotype; and age and gender for sulfotransferase, which the current invention is not directed to (see specification at page 19, lines 26-27).

Therefore, claims 42, 45, 46, and 90-94 are rejected on the grounds that they contain new matter.

Written Description:

Claims 41, 44, 90, and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While Applicant describes a method of administering the probe substrate (caffeine) and measure metabolites to determine the acetylator phenotype by evaluating the enzyme activity of an individual, Applicant does not describe any method of calculating the specific dosage based upon said phenotype (see Figs. 20, 23, 24, and 28).

Scope of Enablement:

Claims 41, 90, and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant is enabled to individualize therapy for an individual having a condition treatable with amonifide by determining NAT2 metabolic phenotype of said individual by using caffeine as a probe to determine acetylator phenotype, then developing a dosing scale based on metabolic ratio (see specification p. 217-223 and 224-230). However, Applicant is *not* enabled to determine the metabolic phenotype of any enzyme to individualize treatment with any N-(aryl substituted)-naphthalidimide compound.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) Nature of the invention.
2) State of the prior art.
3) Level of predictability in the art.
4) Relative skill of those in the art.
5) Amount of direction or guidance provided by the inventor.
6) Presence or absence of working examples.
7) Breadth of the claims.
8) Quantity of experimentation necessary to make or use the invention based on the content of the disclosure.

The instant specification fails to provide guidance that would allow the skilled artisan to

practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1) The nature of the invention.

The claimed invention relates generally to chemotherapy and customizing a treatment regimen, and specifically to methods for individualizing said treatment regimen by determining an individual's specific metabolic phenotype.

2) State of the prior & 3) Level of predictability in the art.

While the state of the art is relatively high with regard to determining the acetylator phenotype for and individual using caffeine as a probe substrate for NAT2, the state of the art with regard to determining the phenotype of an individual for enzymes and metabolic pathways in general is underdeveloped. In particular, there is no known method or assay for determining the phenotype of all enzymes or metabolic pathways for an individual. See Ratain et al. (Cancer Research 1993, 53: 2304-2308) and Wainer et al. (U.S. Patent 5,830,672).

Also, the art of phenotyping involves a very high level of unpredictability. The lack of significant guidance from the present specification or prior art with regard to the actual determination of a metabolic phenotype in an individual, with the claimed method makes practicing the claimed invention unpredictable. By Applicant's own admission (see p. 4 of specification for example), drug metabolizing enzymes have broad specificities and their ability to metabolize a wide variety of molecules creates the potential for many drug interactions and adverse side effects.

4) Relative skill of those in the art.

The relative skill of those in the art is high, generally that of a PHD or MD.

5) Amount of direction or guidance provided by the inventor & 6) Presence or absence of working examples.

The specification at Example II (p. 214-217) and Example III (p. 224-279) teach the specific treatment of metastatic breast cancer with amonifide by determining acetylator phenotype using caffeine as a probe substrate, determining the acetylator phenotype based upon metabolites, then placing individuals into slow, intermediate/slow, or fast acetylators (see specification p. 273) and dosing amonifide accordingly.

7) Breadth of claims.

The claims are very broad and inclusive of determining a metabolic phenotyping general. The breadth of the claims exacerbates the complex nature of the subject matter to which the present claims are directed. The claims are extremely broad due to the vast number of metabolic enzymes and pathways, and their variants. (See Applicant's specification a pages 5-50, for example).

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification does not enable any person skilled in the art to which it pertains (i.e. determining an individual's metabolic phenotype and customizing a treatment based thereupon) to make or use the invention commensurate in scope with the claims. The lack of adequate guidance from the specification or prior art with regard to the actual determination of phenotype of all enzymes (particularly drug metabolizing enzymes) with a probe substrate, fails to rebut the presumption of unpredictability existent in this art.

Applicants fail to provide the guidance and information required to ascertain a metabolic phenotype in general which particular enzyme/metabolic pathway and treatment regimen the claimed method will be effective for without resorting to undue experimentation. Applicant's limited disclosure of using caffeine to determine acetylator phenotype for determining amonifide dosing is noted but is not sufficient to justify claiming all metabolic phenotypes broadly.

In light of the fact that there is no known way to determine one's metabolic phenotype for all enzymes, the mere recitation of "metabolic phenotype" in general is insufficient to enable one of ordinary skill in the art to practice the instant invention with regard to a total metabolic profile. In order for the skilled artisan to practice the instant invention with respect to "metabolic phenotype" in general, there would be an undue burden of determining the phenotype other than those associated with NAT2 acetylator phenotype, as described in the present application.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41 and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41 and 90 are drawn to a method of using a metabolic phenotype to individualize a treatment regimen. However it is not specified what condition (i.e. what types of cancer) is to be treated, rendering the claims indefinite.

Claims 43 and 46 are drawn to a method of characterizing a metabolic phenotype by administering a probe substrate specific to a metabolic pathway. Claims 43 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the specific enzyme for which the probe substrate is specific to.

Summary

Claims 41-46 and 89-94 are rejected. No claims are allowed.

Contact Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is (571) 272-2765. The examiner can normally be reached on Monday-Friday, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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